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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/622,284	08/15/2000	Takumi Sasaki	20-4736P	9843

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EXAMINER	
DEVI, SARVAMANGALA J N	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 03/02/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	Application No. 09/622,284	Applicant(s) SASAKI ET AL.	
	Examiner S. Devi, Ph.D.	Art Unit 1645	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 05 January 2005 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☐ The reply was filed after a final rejection, but prior to filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____ months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The reply was filed after the date of filing a Notice of Appeal, but prior to the date of filing an appeal brief. The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☒ Applicant's reply has overcome the following rejection(s): See attachment.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: *None*.
   Claim(s) objected to: *None*.
   Claim(s) rejected: *1,3,5 and 9-13*.
   Claim(s) withdrawn from consideration: *6 and 7*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☐ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: _____.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☒ Other: See attachment.

ATTACHMENT TO ADVISORY ACTION

Applicants' After-final Amendment

1) Acknowledgment is made of Applicants' after-final amendment filed 01/05/05 in response to the final Office Action mailed 07/09/04. The amendment has been entered.

Status of Claims

2) Claims 1, 3, 5, 9 and 13 have been amended via the amendment filed 01/05/05.

Claims 1, 3, 5-7 and 9-13 are pending.

Claims 1, 3, 5 and 9-13 are under examination.

Prior Citation of Title 35 Sections

3) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

4) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Objection(s) Withdrawn

5) The rejection of claim 1 made in paragraph 33 of the Office Action mailed 07/09/05 is withdrawn in light of Applicants' amendment to the claim.

Rejection(s) Withdrawn

6) The rejection of claims 1, 3, 5 and 9-13 made in paragraph 28 of the Office Action mailed 07/09/04 under 35 U.S.C. § 112, first paragraph, as containing inadequate written description, is withdrawn in light of Applicants' amendments to the claims and/or the base claim(s).

7) The rejection of claims 1, 3, 5 and 9-13 made in paragraph 29 of the Office Action mailed 07/09/04 under 35 U.S.C. § 112, first paragraph, as containing new matter, is withdrawn in light of Applicants' amendments to the claims and/or the base claim(s).

8) The rejection of claims 1, 5 and 9 made in paragraph 30(a) of the Office Action mailed 07/09/04 under 35 U.S.C § 112, second paragraph, as being indefinite, is for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

9) The rejection of claim 13 made in paragraph 30(b) of the Office Action mailed 07/09/04

under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

10) The rejection of claim 1 made in paragraph 30(c) of the Office Action mailed 07/09/04 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

11) The rejection of claims 1, 3, 5 and 9 made in paragraph 30(d) of the Office Action mailed 07/09/04 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the base claim.

12) The rejection of claims 3, 5 and 9-13 made in paragraph 30(e) of the Office Action mailed 07/09/04 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the base claim.

Rejection(s) Maintained

13) The rejection of claims 1, 3, 5 and 9-13 made in paragraph 32 of the Office Action mailed 07/09/04 under 35 U.S.C. § 102(b) as being anticipated by Kappler *et al.* (WO 93/14634 - already of record), is maintained for reasons set forth therein and herebelow.

Applicants acknowledge that: (a) Kappler ('634) discloses 'the preparation of modified (mutations)/derivatives of SEB'; and (b) Kappler discloses a technique for reducing toxicity of SEB when administered into a living body'. However, Applicants submit the following with regard to Kappler's disclosure:

(a) Kappler fails to suggest or disclose that such SEB modifications with reduced toxicity could be used for prophylaxis/remedy of autoimmune diseases such as rheumatoid arthritis, ulcerative colitis, etc. with high safety;

(b) The description of Kappler on pages 12-14 and 17 discloses that the modifications of SEB interact with the vβ elements of T cell receptors in a way which leads to modifications in the way T cells respond to a superantigen, including deletion or inactivation/desensitization of T cells as well as enhancing T cells. At lines 20-24 of page 14, Kappler specifically discloses that 'The molecules of this invention can function in this manner, i.e., by leading to deletion or inactivation/desensitization of at least one or more subpopulations of T cells which present a particular vβ element';

(c) Kappler differs from the present invention which recites in the claims the limitation: 'without inducing elimination of T cells having specific vβ components, the elimination being normally induced by natural type SEB';

(d) Examples 6 and 7 of the present invention show that the SEB modifications are efficacious by oral administration. Prior to the present invention, orally administered modified SEBs have never been disclosed nor suggested in the prior art which was due to the fact that SEB might be a cause of certain diseases such as food poisoning;

(e) Kappler fails to suggest or disclose the SEB modifications as described in limitations a), b) and c) of claim 1.

Applicants' arguments have been carefully considered, but are not persuasive for the following reasons. The sequence of Office's rebuttal below corresponds to Applicants' arguments as set forth above:

(a) As set forth in paragraph 31 of the Office Action mailed 07/09/04, instant claims are not drawn to a method of treating an autoimmune disease, such as, rheumatoid arthritis, by oral administration of the modified SEBs with reduced toxicity of the instant invention. Instead, the instant claims are drawn to a prophylactic comprising SEB having a substitution of at least one amino acid residue at position 23, 44 or 9 wherein the substitution is with an amino acid other than asparagine, phenylalanine or aspartic acid respectively, and wherein said SEB interacts with specific vβ component of TCR but is reduced in immunological responsiveness to SEB as recited. The term 'prophylactic/remedy for immunopathy' represents intended use of the claimed product. The structural requirement of the base claim, for example, is that the claimed SEB has at least one amino acid substitution within the amino acid sequence of natural type SEB wherein the substitution is at position 23, 44 or 9 wherein the substitution is with an amino acid other than asparagine, phenylalanine or aspartic acid respectively. Kappler's SEB mutants meet this structural requirement of the claim(s). Kappler taught these SEB mutants for use as a prophylactic or therapeutic product, and vaccines, wherein the mutant superantigens interact with specific Vβ elements of T cell receptors (TCR) and elicit immune response without inducing T cell proliferation. See abstract; claims; and page 16, lines 25-29. The recitations such as 'for immunopathy' and 'for oral administration' represent the intended use of the claimed product. A

recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See *In re Casey, 152 USPQ 235 (CCPA 1967)* and *In re Otto, 136 USPQ 458, 459 (CCPA 1963)*. The recitation "for immunopathy" is not given any patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao, 535 F.2d 67, 190 USPQ 15 (CCPA 1976)* and *Kropa v. Robie, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951)*.

(b) Kappler's disclosure at lines 11-14 on page 17 states that the molecule of their invention interacts with at least one Vβ element on T cell receptors, which is an indication that Vβ-containing T cells are not eliminated. The last two lines of page 17 of Kappler state that the modification of the T cell response can involve stimulation of T cell subpopulations thus indicating the lack of elimination of T cells.

(c) Although Kappler *et al.* do not expressly recite all the functional properties of their modified SEBs, including, inhibitory activity on T cell activation; interaction with specific Vβ component of T cell receptor; and reduced immunological responsiveness without inducing elimination of T cells having specific vβ components, these functional limitations represent the inherent properties of Kappler's modified SEBs. Because of the identical structure and the identical bacterial origin of the prior art prophylactic or therapeutic modified SEBs, the prior art modified SEBs are viewed as the same as the modified SEBs claimed in the instant claims, and therefore these modified SEBs are expected to have the same intrinsic functional properties as that of the Applicants' modified SEBs. The Office's position that the prior art modified SEBs are the same as Applicants' modified SEBs, is based upon the fact that every characteristic overlapping in the prior art modified SEBs and the Applicants' disclosure are the same. In spite of the fact that the prior art is silent about all of the disclosed functional characteristics of the Applicants' modified SEBs, there

is sufficient overlap to reasonably conclude that the prior art modified SEBs are one and the same as the Applicants' SEBs. Since the prior art modified SEBs are structurally the same as the SEBs claimed in the instant claims, the prior art SEBs are expected to have the prophylactic capacities or properties that are recited in the instant claims. The functional properties are viewed as the intrinsic functions inseparable from the modified SEBs of the prior art.

(d) The recitation "for oral administration" is not given any patentable weight because the recitation occurs in the preamble. The recitation represents the intended use of the claimed product. A recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See *In re Casey, 152 USPQ 235 (CCPA 1967)* and *In re Otto, 136 USPQ 458, 459 (CCPA 1963)*. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao, 535 F.2d 67, 190 USPQ 15 (CCPA 1976)* and *Kropa v. Robie, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951)*.

Furthermore, Kappler taught the mode of administration to include all of the standard methods of administering therapeutic agents to a subject (see first paragraph on page 19) and therefore includes oral administration.

Contrary to Applicants' assertion, it appears that modified staphylococcal enterotoxins or SEB derivatives comprised in physiological salt solution have been administered previously in the art as oral preparations for preventing and treating immunopathy diseases including rheumatoid arthritis or ulcerative colitis. See for example, the abstract of JP 09110704 A (Applicants' IDS). (e) Applicants do not elaborate on the statement that Kappler fails to suggest or disclose the SEB modifications as described in limitations a), b) and c) of claim 1. Kappler specifically disclosed the SEB mutants of the instant invention. For instance, Kappler disclosed SEB mutants, BC-6, BC-66 and BC-88, carried isoleucine, tyrosine and lysine residues respectively at position 23 of SEB, whereas the mutant BR-291 carried serine at position 23 of SEB (see Tables II and III; and page

27). While Kappler's SEB mutants, BR-267 and BA-50, carried serine at position 44 of SEB, the mutant BA-53 carried leucine at position 43 of SEB (see Tables II and III). Kappler *et al.* also disclosed a SEB mutant, BR-257, which carried asparagine in place of aspartic acid at position 9 of SEB (see Figure 3 and last paragraph on page 27).

In sum, where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established. *In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977)*. "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990)*. Therefore, the *prima facie* case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. *In re Best, 562 F.2d at 1255, 195 USPQ at 433*. Kappler's disclosure anticipates the instant claims. The rejection stands.

Remarks

14) Claims 1, 3, 5 and 9-13 stand rejected.

15) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center, which receives transmissions 24 hours a day and 7 days a week. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The RightFax number for submission of amendments, responses or papers is (571) 273-8300.

16) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.Mov. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

17) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to

Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

March, 2005

S. DEVI, PH.D.
PRIMARY EXAMINER